LAW OFFICES
HYMAN, PHELPS & MCNAMARA, P.C.

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A. WES SIEGNER, JR.
SAMIA N. RODRIGUEZ
ALAN M. KIRSCHENBAUM
ROBERT T. ANGAROLA
(1945-1996)

700 THIRTEENTH STREET, N.W.
SUITE 1200
WASHINGTON, D. C. 20005-5929
(202) 737-5600
FACSIMILE
(202) 737-9329

2603 MAIN STREET
SUITE 650
IRVINE, CALIFORNIA 92614-4260
(949) 553-7400
FACSIMILE
(949) 553-7433

DIRECT DIAL
(202) 737-4283

DOUGLAS B. FARQUHAR
OF COUNSEL

MARY BETH NERAAS
JENNIFER B. DAVIS
JOHN A. GILBERT, JR.
FRANCES K. WU
DAVID B. CLISSOLD
KATE DUFFY MAZAN
HOLLY M. BAYNE*
CASSANDRA A. SOLTIS*
JOSEPHINE M. TORRENTE*
ERIC E. ROGERS*
MICHELLE L. BUTLER*
*NOT ADMITTED IN D.C.

April 14, 1999

BY HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: FDA Docket No. 98D-0785; Draft Guidance for Industry on Developing Medical Imaging Drugs and Biologics

Dear Sir or Madam:

These comments on the Food and Drug Administration's ("FDA's") October 1998 "Draft Guidance for Industry: Developing Medical Imaging Drugs and Biologics" ("Draft Guidance") are submitted on behalf of the Medical Imaging Contrast Agent Association ("MICAA"). MICAA is a recently formed trade association of companies involved in the research, development, manufacturing and distribution of medical imaging drug products in the United States. The chief purpose of MICAA is to characterize and communicate the medical benefits, appropriate utilization, and cost-effective uses of medical imaging drug products.

MICAA representatives participated in FDA's March 26, 1999 public meeting on the Draft Guidance. MICAA also submitted "Talking Points" to FDA in advance of the March 26 meeting.

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MICAA commends FDA for its efforts to establish a guidance for medical imaging drugs, and appreciates the opportunity to participate in the development of Agency policy in this area. The comments that follow expand on the issues discussed in MICAA's talking points and at the March 26 meeting. At the meeting, FDA officials indicated that significant changes are likely to be made to the Guidance as a result of public feedback. As requested in its letter of April 1, 1999, MICAA urges FDA to propose these changes in a new draft for further, abbreviated public comment before issuing a final guidance.

I. Medical Imaging Drugs Are Not the Same as Therapeutic Pharmaceuticals

In the Draft Guidance, FDA refers to numerous ICH and FDA guidance documents which set forth safety and efficacy considerations for therapeutic drug products.[1] In many respects, FDA's approach to safety and efficacy demonstrations for medical imaging drug products closely parallels its approach to the establishment of safety and efficacy for therapeutic drugs.

A critical point that MICAA wishes to emphasize, and that underlies many of the specific issues discussed below, is that the physical, chemical and biological properties of medical imaging drug products, as well as the significance of those properties, are distinctly different from those of therapeutic pharmaceuticals. For medical imaging drugs, physics and physical chemistry are as important (if not more important) than biology and biochemistry. Unlike therapeutic drug products, the clinical usefulness of a medical imaging drug is not directly related to the drug's in vivo effects.

In addition, the manner in which physicians use medical imaging drug products, and the benefits that medical imaging drugs afford to patients, are quite different from how physicians use, and patients benefit from, therapeutic drugs. Certain classes of medical imaging drugs are typically administered in small mass doses for single or limited repeat use, and they are rapidly eliminated from the body, as illustrated in the following tables:

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[1] See, e.g., Draft Guidance at 17-19, 21, 23, 25, 36.

TABLE 1

Comparative Mass Dose Ranges

Modality	Component	Amount (Single Use)
Nuclear	**^{99m}Tc complex** **Ligand, carrier**	**1 – 10 ng** **0.01 – 10 mg**
Ultrasound	**Gas** **Shell material**	**0.2 – 2.0 mg** **0.5 – 10 mg**
MRI	**Gd^{+3}- complex** **Ligand**	**2 – 12 gm** **0.01 – 0.50 gm**
X-ray	**Iodinated moiety** **Excipients** **0.05% Impurity**	**15 – 150 gm** **1.5 – 100 mg** **7.5 – 75 mg**

TABLE 2

Representative Comparative Elimination

Modality	Component	Elimination
Nuclear	**^{99m}Tc complex**	**100%*** **$t_{1/2}$ = 361.2 min**
Ultrasound	**Gas**	**96 +/- 23%**** **$t_{1/2}$ =1.3 +/- 0.7 min**
MRI	**Gd^{+3}- complex**	**95 +/- 5%** **$t_{1/2}$ = 196 +/- 6 min**
X-ray	**Iodinated moiety**	**97 +/- 2%** **$t_{1/2}$ = 123 +/- 8 min**

* The 100% elimination reported for nuclear medicine products applies to the tracer itself where a combination of physical and physiological processes occurs. The pharmacokinetics (ADME) of the ligand may be quite different.

** The elimination reported for ultrasound is based on the only product that is currently FDA-approved, Optison. Other microbubbles and microaerosomes which are formulated with air and/or gases other than octaflouropropane will have different elimination values.

Given these distinctions, MICAA believes that it is inappropriate to apply to medical imaging drugs the same or similar measures of safety and efficacy typically applied to therapeutic pharmaceuticals.

II. Group I Status of Medical Imaging Agents

A. Criteria for Group 1 Designation

The Draft Guidance states that "Medical imaging drugs classified as *Group 1 medical imaging drugs* may be able to undergo a more efficient clinical safety evaluation during development" whereas "*Group 2 medical imaging drugs* should undergo a complete clinical safety evaluation."[2] In addition, the Draft Guidance states that "[f]or Group I medical imaging drugs, reduced safety monitoring in Phases 2 and 3 of drug development is justified" unless toxicity is noted, in which case "appropriate clinical safety monitoring should be performed."[3] To be included in Group 1, the Draft Guidance says that non-clinical laboratory testing must demonstrate a no-observable-effect level (NOEL) of at least 1,000 times (adjusted for the animal species) the maximum dose and dosage to be used in human studies, and that the NOEL should be determined in expanded-acute, single-dose toxicity studies, short-term, repeated-dose toxicity studies, and safety pharmacology studies.[4] Any medical imaging drug that does not meet the criteria for Group 1 is considered to be in Group 2.[5]

MICAA believes that the requisite safety factor of 1,000 times the maximal human dose would effectively mean that no medical imaging drug could qualify for Group 1 status. In many cases, it simply would not be physically possible to administer the amount of drug necessary to achieve this dose to test animals. Moreover, many currently approved medical imaging drugs would likely produce observable effects at such extreme doses, assuming it were possible to administer these doses to animals.

At a January 26, 1999 public meeting between representatives of FDA and the Council on Radionuclides and Radiopharmaceuticals ("CORAR") concerning the Draft

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2 Id. at 34 (emphasis in original).

3 Id. at 35.

4 Id. at 34-35.

5 Id. at 36.

Guidance, FDA officials suggested that a product could be concentrated in order to introduce into animals the high doses of drug substance necessary to test for a 1,000x safety margin.[6] As explained in CORAR's comments on the Draft Guidance, this approach is problematic for radiopharmaceuticals, since their performance can change if the physical chemistry of the injected drug product is altered by concentration.

The performance of various contrast agents may similarly be changed when the injected drug product is altered by concentration. For example, the colligative properties, osmolality and viscosity of solutions will be altered by concentration. In certain cases, such as for iodinated x-ray contrast agents, differences in osmolality and viscosity can profoundly effect both the safety and efficacy of a product. Also, magnetic resonance potency or relaxation enhancement is dependent upon the amount of paramagnetic chelate per unit volume of solution. Furthermore, paramagnetic chelates affect both T1 (spin-lattice) and T2 (spin-spin) relaxation times. Signal intensity can either be increased or decreased in a given image depending on the acquisition technique/relative contribution of T1 and T2 effects, as well as the amount of the paramagnetic chelate administered. These properties would be altered by concentration. Finally, the image enhancement effects caused by stabilized microbubbles, microaerosomes and other related particulate contrast media for ultrasound are dependent upon bubble size, size distribution and concentration. Obviously, these effects will be altered by concentration.

In its comments on the Draft Guidance, CORAR discusses additional problems with FDA's criteria for Group 1 designation, including the requirements for both expanded-acute, single-dose toxicity studies and repeat-dose toxicity studies in animals. The points made in CORAR's comments may be equally valid for other medical imaging drugs, particularly the intravenously administered microbubbles, microaerosomes and other related microparticles used in diagnostic contrast sonography. These biologically inactive drugs are administered in low mass doses, typically in milligram quantities, in conjunction with an imaging examination.[7] Also, like radiopharmaceuticals, gaseous ultrasound contrast agents are eliminated from the body rapidly and completely – indeed, even more rapidly than radiopharmaceuticals.[8] There is little opportunity for such drugs to accumulate to toxic levels. The frequency of use of ultrasound agents is also limited to single-dose or

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6 See January 25, 1999 Meeting Transcript at 23, 29.

7 See Section I, Table 1, above.

8 See Section I, Table 2, above.

limited repeat-dose administration. Despite these attributes, the proposed safety factor of 1,000 would preclude designation of such contrast agents as Group 1 medical imaging drugs.

MICAA requests that FDA reevaluate its criteria for Group I designation. In its comments, CORAR has proposed an alternative set of criteria for Group 1 designation based on a safety factor of 25 established in expanded single-dose studies, or of five established in repeat-dose studies. MICAA supports the CORAR criteria and believes they are equally applicable to non-radiopharmaceutical imaging drugs, particularly ultrasound contrast agents. MICAA urges FDA to adopt these criteria.

B. New Routes of Administration for Non-Systemically Absorbed Agents

The Draft Guidance indicates that there may be special characteristics of medical imaging drugs that could allow nonclinical and clinical safety assessments to be "relatively efficient" or "tailored." These special characteristics include dose, mass, route of administration, frequency of use, and biological, physical, and effective half-lives.[9] The Draft Guidance also states that Group 1 designation may be based on a history of sufficient clinical use or previous clinical trial experience demonstrating no clinically detectable allergic, immunologic, biochemical, physiologic, or pharmacologic responses, and no dose-related toxicological risk or adverse event profile, at clinical doses or dosages.[10]

In some cases, sponsors of contrast agents develop an approved agent for an alternate route of administration. For example, a Gd+3 chelate approved for intravenous use in MR imaging might be developed for alternate routes of administration (oral, rectal, intraarticular, etc.).[11] Under the Draft Guidance, it would appear that the history of intravenous use could qualify the agent for Group 1 designation. Moreover, if it has been shown that there is virtually no systemic absorption via these alternate routes, it would appear that this information, in conjunction with the safety profile of intravenous use, would constitute a sufficient safety evaluation. MICAA requests clarification on the role that route of administration and lack of systemic absorption might play in "tailoring" the nonclinical and clinical safety assessment in these circumstances.

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9 Draft Guidance at 15, 34.

10 Id. at 35.

11 Approval under an abbreviated NDA may not be possible for such an agent where a new indication is sought.

C. Redesignation Between Group 1 and Group 2

The Draft Guidance does not specify the procedures by which Group 1 designations will be made. MICAA recommends that FDA establish procedural guidelines so that sponsors know when to request designation and what types of information should accompany the request, and so that the designation process is applied consistently. MICAA supports CORAR's position that sponsors should be permitted to request and obtain Group 1 status prior to Phase I based on a demonstration, through pre-clinical studies, that the Group 1 criteria are met, subject to withdrawal of Group 1 status if subsequent clinical tests demonstrate any significant toxicity. MICAA also urges FDA to clarify that, just as a Group 1 medical imaging drug can be redesignated as Group 2, a Group 2 imaging drug whose further non-clinical and early clinical testing demonstrates that it meets the Group 1 criteria can be redesignated as Group 1.

At the March 26 meeting, FDA indicated that Group 1 drugs are not the only medical imaging drugs eligible for "tailored" safety testing, and that the testing program for Group 2 drugs could also vary based on the drug's safety-related characteristics. MICAA urges FDA to clarify this point in the Guidance.

III. The Role of Clinically Blinded Readings

The Draft Guidance notes that "[i]n studies that are intended to demonstrate efficacy of a medical imaging drug, evaluations of images should be performed by readers that are both *independent* and *blinded* . . . "[12] MICAA appreciates the importance of minimizing bias in the efficacy evaluation. However, MICAA disagrees with, and requests that FDA reevaluate, certain of the reader characteristics and blinding criteria proposed in the Draft Guidance.

A. Independence

According to the Draft Guidance, "independence" means that a reader cannot have participated in Phase 3 studies, and cannot be affiliated with the sponsor or with institutions where the studies were conducted.[13] MICAA submits that the requirement that a reader not be affiliated with an institution where the study was conducted is too onerous. It is often difficult to find readers with enough experience and expertise to evaluate new agents,

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12 Draft Guidance at 25 (emphasis in original).

13 Id.

especially in large trials. MICAA suggests that FDA allow blinded readers to come from the same institution as an investigator if they are not involved in the study. FDA should also consider that there may be circumstances in which it would be appropriate to allow investigators to read images that are obtained from study sites other than their own. Such modifications to the independence requirement would facilitate selection of appropriate readers without introducing undue bias into the efficacy evaluation.

B. Clinical Blinding

As defined in the Draft Guidance, "blinded" means that the reader must be unaware of the treatment/agent that was used to obtain an image, and must have limited or no knowledge of patient-specific clinical information and the study protocol.[14] At the March 26 meeting, FDA indicated that the Agency has reconsidered the requirement that efficacy be based solely on studies in which readers receive little or no information about the patient or the study protocol. Dr. Mills described a sequential unblinding methodology, modeled after a grand rounds, in which images would first be presented to a reader with "full blinding," and then with complete clinical information and all supporting imaging studies (as prospectively designated in the protocol), but no outcome information. Dr. Mills explained that, for standardized imaging such as x-ray, the "full blinding" in step 1 would mean that no clinical or technical information would be provided, while for new or non-standardized imaging with radiopharmaceuticals or other agents, the "full blinding" in step 1 could be modified so that anatomical orientation and detail, and certain prospectively defined clinical information, could be provided to the reader. Dr. Mills also acknowledged that blinded or sequential readings may not be appropriate for all products, and that, for contrast agents, the Agency would entertain the possibility of studies in which independent readers are provided with substantial clinical/anatomical information (but not final outcome or "truth"), as long as the information provided is prospectively defined in the imaging protocol.

MICAA supports FDA's departure from a strict adherence to full blinding as the only acceptable way to measure efficacy of medical imaging drugs. As MICAA and CORAR representatives explained at length at the public meetings and in their prior submissions to FDA, such readings, while capable of reducing bias in a statistical sense, do not represent the effectiveness of the agent as it will perform in any defined clinical setting. This is because the fully blinded reader is not familiar with the agent and the imaging equipment, and lacks basic information on the anatomy, positioning, and condition of the

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[14] Id.

patient that is essential to render an interpretation. As a result, the data generated by such readings have limited utility to clinicians (not to mention third party payors). MICAA believes that physicians who use medical imaging drug products are better served by having information that will enable them to evaluate, and make appropriate clinical use of, medical imaging products. This requires that a product be tested under conditions that are consistent with the manner in which the physician will use the drug, and that the results of such testing be conveyed to the physician in product labeling.

Although MICAA supports FDA's departure from exclusive reliance on full clinical blinding as the basis for efficacy evaluation, MICAA disagrees with the sequential unblinding model as applied to most contrast agents. The sequential unblinding model could result in the generation of at least seven data sets: the pre-contrast alone, post-contrast alone, and paired readings in step one (fully blinded) independent readings; the same three types of readings in step two (informed) readings; and the on-site investigator readings. The multiplicity of data sets could introduce confusion into the review process, with likely disagreement between the sponsor and FDA on the relative weights to be accorded to each data set. Moreover, the sheer number of readings would – in addition to significantly increasing the costs of studies – pose problems for recruitment of competent readers and the establishment of reading schedules that avoid reader fatigue, especially in large trials.

MICAA believes that fully blinded readings may be appropriate in cases where: (1) the unenhanced images have sufficient anatomic detail to provide a medical context for accurate interpretation (e.g., chest x-ray, certain CTs and MRIs); (2) the imaging modality and technique(s) are highly reproducible and have low interexamination variability (i.e., from patient to patient, instrument to instrument, practitioner to practitioner; or (3) the indication is primarily based upon interpretive criteria (e.g., number of lesions, density, intensity, CNR).

However, for most contrast agents, the effectiveness evaluation should be based on selectively informed readings in which readers are provided with the following information:

- prospectively defined demographic information (e.g., age and sex)
- physical examination results as appropriate
- results of diagnostic tests (e.g., ECG) other than similar imaging tests
- essential information on image acquisition technique (e.g., pulse sequence, pre- or post-contrast, temporal sequence)

- the anatomical region of interest if not obvious (especially for ultrasound and nuclear agents)

Readers in such studies should not be provided with the following information:

- the "Truth" (or Standard of Reference) measure
- no or limited information on the study protocol
- dose
- identity of drug (test drug, comparator, placebo)
- method of administration
- inclusion/exclusion criteria

At the March 26 meeting, FDA requested that MICAA and CORAR provide proposed decision trees showing, for the various indication categories, the types of readings (e.g., fully blinded, selectively informed, fully informed) that should be performed. MICAA is currently developing a decision tree in response to FDA's request, and intends to submit it to the docket within two weeks from the date of these comments.

C. Labeling

In discussions among representatives of FDA, MICAA and CORAR, Agency officials solicited suggestions on how information from blinded and unblinded readings should be presented in the labeling. MICAA believes that data on each type of reading should be permitted to be presented for each major endpoint.

Clinical investigations of contrast imaging agents typically involve one or more of the following types of endpoints: (1) imaging evaluation endpoints; (2) diagnostic performance; and (3) radiologic patient management endpoints. Image evaluation may involve measuring signal intensity or enhancement patterns, determining whether the images are otherwise technically adequate, or counting the number of lesions/vessels/heart segments appearing on the image. Diagnostic performance endpoints involve measuring sensitivity/specificity, positive predictive value/negative predictive value, or confidence in the diagnosis. Patient management endpoints involve determining whether the image assisted in making the diagnosis, or whether it had an impact on radiologic and clinical patient management.

MICAA believes that the "Clinical Trials" section of the package insert should present data for each of these types of endpoints that is studied in the trials, from on-site investigator readings and from blinded readings. The latter may be independent, selectively

informed readings as described in Section III. B, above, or fully blinded readings, or both. The following grid is an example for a product seeking a disease-specific indication. (Note that outcome measures would change depending on the indications that are being sought.)

Clinical Trials:

	Study A		Study B	
Outcome Measure	Institutional Readings	Blinded* Readings	Institutional Readings	Blinded* Readings
Image Evaluation				
Diagnosis				
Patient Management				

* May be fully blinded, or selectively informed (as described in Section III. B.), or both.

IV. Indications for Medical Imaging Drugs

The Draft Guidance identifies four categories of claims for medical imaging drugs: structure delineation; functional, physiological, or biochemical assessment; disease or pathology detection or assessment; and diagnostic or therapeutic patient management.[15] It also acknowledges that these categories need not be mutually exclusive,[16] and that a single study may be sufficient to support more than one type of claim.[17]

Given that multiple indications for a medical imaging drug may be possible, FDA's Guidance should include more detailed information on how a single trial might be designed

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15 Draft Guidance at 3.

16 Id. at 4.

17 See id. at 7-8 discussing the example of an ultrasound contrast drug for assessment of stenotic blood vessels.

to satisfy the data requirements for multiple indications. For example, the ability of a contrast agent to demonstrate normal myocardial perfusion might be used to support a "physiological assessment" indication. The ability of the same contrast agent to demonstrate deficient perfusion in an adjacent segment might be used to support a "disease diagnosis" indication. The ability of the contrast agent to demonstrate either normal or abnormal perfusion might be used to support a patient management indication to the extent that such information aids a physician in determining the appropriateness of cardiac catheterization. It is conceivable that all three of these endpoints could be established in the same clinical trial. MICAA requests that FDA clarify that this would be permissible, and provide guidance on how such a trial could be designed (e.g., using multiple small cohorts).

V. Establishing Claims for Medical Imaging Drugs

A. Clinical Usefulness

The Draft Guidance states that "claims for medical imaging drugs should be supported with information demonstrating that the potential benefits of the use of a medical imaging drug outweigh the potential risks to the patient."[18] According to the Draft Guidance, potential risks include the risks of incorrect diagnostic information which may lead to inappropriate decisions in diagnostic or therapeutic management.[19] MICAA submits that in practice, it will be difficult and perhaps inappropriate for sponsors to anticipate the risk/benefit evaluation that a physician must make in deciding whether to use a medical imaging drug in the examination of a particular patient. While sponsors can – and do – provide information on the potential benefits and risks of their products, they cannot determine what level of increased diagnostic information available to the physician outweighs a given level of safety risk.

The Draft Guidance also states that a clinically useful medical imaging drug "provides information that contributes to the appropriateness of diagnostic or therapeutic patient management, contributes to beneficial clinical outcome, or provides accurate prognostic information."[20] It is not clear that the first two indication categories identified by FDA for medical imaging drugs – structure delineation and functional, physiological, or biochemical assessment –would be encompassed in this description. In particular, the

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18 Draft Guidance at 8-9.

19 Id. at 9.

20 Id.

delineation of a structure (post-contrast) where none was previously seen (pre-contrast) is often the main purpose of a contrast imaging examination (e.g., conventional angiogrophy). As FDA recognizes in the "Indications" section of the Draft Guidance,[21] structural delineation has value in its own right, and has been the basis for product approval in the past. FDA should clarify that a contrast agent developed for a structural delineation indication would fall within FDA's description of clinical usefulness provided that the measures of clinical usefulness are prospectively and objectively defined in the protocol, and subsequently statistically validated.

The Draft Guidance also states that, "for a contrast drug product to be considered clinically useful, the product used in combination with an imaging device should provide useful information beyond that obtained by the imaging device alone." In other words, "imaging with the contrast drug product should add value when compared to imaging without the contrast drug product."[22] This definition of "clinical usefulness" is problematic for a number of reasons.

First, certain active control trials may not include an evaluation of the "imaging device alone." Second, a medical imaging drug may permit similar or substantially the same information to be acquired in less time as compared to the imaging device alone. This would fail the requirement for "information beyond that obtained by the imaging device alone." Third, the definition fails to take into account the potential clinical usefulness of a study in which there is no demonstrable difference between the pre-contrast and post-contrast images. For example, in MRI examinations performed after intravenous administration of a Gd^{+3}-chelate, lack of contrast enhancement can be indicative of little or no disruption of the blood brain barrier. This is often associated with a lower grade of malignancy. In these situations particularly, measures of diagnostic confidence may be helpful.

At the March 26 meeting, an FDA representative appeared to agree that the usefulness of an imaging drug should not necessarily be tied to its ability to provide information beyond that obtained by the imaging modality alone. MICAA recommends that FDA clarify this point in the Draft Guidance.

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21 Id. at 4.

22 Id. at 9.

B. Defined Clinical Settings

The Draft Guidance suggests that each of the defined clinical settings in which a medical imaging drug is intended to be used should be evaluated in a separate clinical trial.[23] However, indications for contrast media are usually general and not disease-specific. A liver imaging agent, for example, may offer improved detection of liver lesions. The Guidance implies that two pivotal studies would be required for each setting in which detection of liver lesions could be clinically important – e.g., incidental liver lesions, liver lesions in cases of known metastasis, and liver lesions in follow-up. This would not only be impractical but also unnecessary. When an agent is not organ or disease specific, e.g., barium or iodinated compounds, and is intended to image structure only, clinical setting-specific evaluations are not useful since pathology does not vary based on clinical etiology. Only when an imaging drug's mechanism of action varies with the pathophysiology of the disease process does it make sense to perform studies on the different clinical populations in which the drug is intended to be used.

MICAA notes that, for radiopharmaceuticals, the Food and Drug Administration Modernization Act of 1997 (FDAMA) requires FDA to permit labeling indications to refer to manifestations present in several disease states.[24] The intent of this provision was to enable sponsors to seek an indication that refers to a general manifestation rather than a specific disease, without conducting separate studies for each disease associated with the manifestation. Although this provision does not apply to contrast agents, there does not appear to be a scientific basis for distinguishing between radiopharmaceuticals and contrast agents in this regard. FDA should revise its Draft Guidance to account for the "general" clinical setting in which certain medical imaging agents are used.

VI. Truth Standards

The Draft Guidance defines a "truth standard" as "an independent way of evaluating the same variable being assessed by the investigational drug. A truth standard is known or believed to give the true state of a patient or true value of a measurement. Truth standards

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23 Id. at 10.

24 FDAMA § 122(a)(2).

are used to demonstrate that the results obtained with the medical imaging drug are valid and reliable."[25]

MICAA acknowledges the importance of ensuring that results obtained with medical imaging drugs are valid and reliable. However, in some cases, the use of truth standards may be difficult or impossible. In certain cases, truth standard methods may be more invasive or risky than the drug under investigation. For example, measurements of coronary artery stenosis – e.g., MRI coronary angiography using intravenous administration of contrast, echocardiography using intravenous administration of contrast, and conventional x-ray angiocardiography – all carry different risks and costs.

In addition, MICAA recommends that FDA more clearly define methods for determining and demonstrating that a truth standard is consistent with accepted clinical practice. For example, FDA should explain how meta-analysis of recent literature could be used to justify the validity of a truth standard. Perhaps it would be appropriate to include information on the sensitivity and specificity of the selected truth standard in the package insert. MICAA recommends that the Guidance also address the often cumbersome, costly, and not often useful practice of being required to essentially "re-validate" the standard of reference (such as CECT) in each study, and address how sponsors might use literature meta-analyses as described above.

The Draft Guidance also states that when a medical imaging drug is being developed for an indication for which other drugs or diagnostic methods are approved, a direct, concurrent comparison to the approved drug or diagnostic method is encouraged.[26] When comparing the test drug with the approved drug, sponsors are further encouraged to use the same truth standard.[27] At the March 26 meeting, an FDA representative stated that sponsors were not obligated to use a comparator product in addition to a truth standard. MICAA requests that this be made explicit in the Draft Guidance.

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As demonstrated above, there are several critical issues that warrant further FDA consideration and public comment. MICAA requests that the Agency consider the above

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25 Draft Guidance at 29.

26 Id. at 30-31.

27 Id. at 31.

comments and issue a new Draft Guidance for public comment before adopting a final guidance.

Respectfully submitted,

Alan M. Kirschenbaum
Counsel to the Medical Imaging
Contrast Agent Association

AMK/dmb